In the Drawings

The attached sheets of drawings includes replacement Figures 1, 9 and 10.

Figure 1 is a better copy. Accordingly, an annotated sheet is not believed necessary.

The dark fill on the bar graphs on Figures 9 and 10 has been removed as indicated on the accompanying annotated sheet.

Attachment: Replacement Sheet for Figure 1

Replacement Sheet for Figure 9 and 10.

Annotated Sheet for Figure 9 and 10.

Remarks

The status of the claims is as follows:

Pending: 57-64, 70-72 and 74-89;
Active: Claims 57, 58, 63, 64, 70-72, 74-80 and 86-89;
Withdrawn: Claims 59-62, and 81-84; and
Canceled: Claims 1-56, 65-69 and 73.

No new matter has been added by the amendments to the specification or claims. The specification has been amended to correct grammar, form or spelling, and to reinsert the abstract as published at the PCT stage as the final page of the specification. Independent claims 57 (active) and 81 (withdrawn) have been amended to correct the font used in the "I" under the chemical structure and also to subscript the numbers in the text listing the chemical constituents. Claim 57 has also been amended to remove the words "or prevention." Claim 77 has been amended to clarify the antecedent basis.

Statement of Substance of the Interview

As required in reply to form PTOL-413, entitled "Interview Summary," for the telephonic interview of April 15, 2009, Applicants provide the following statement of the substance of the interview. Applicants' undersigned representative telephoned Examiner to alert Examiner to the fact that the Office action had been mailed to Applicants' former counsel, and that a Power of Attorney and change of correspondence address to the undersigned had been filed. Examiner confirmed the Power of Attorney and change of correspondence address were in the record, and indicated that, the documents had not yet been processed. Applicants sincerely thank

Examiner for his assistance in expediting the processing of the new power of attorney and change in correspondence address by the Office.

There is one minor correction to the record. Although subsequent to the interview, Applicants' undersigned attorneys did receive a copy of the Office action from Applicants' former counsel, at the time of the interview, Applicants' undersigned attorneys had received a copy of the Office action from Applicants' Polish counsel (not the previous attorneys of record as stated on the interview summary form). Applicants apologize for any confusion.

The Priority Document

Examiner has noted that a translation of Applicants' Polish priority document had not yet been received. Submitted herewith is an English translation of the priority document, P-364348. A statement of accuracy is on the bottom of every page of the translation.

Request for consideration of IDS document DE 840698C

Examiner notes that he did not consider IDS document DE 840698 C (or DE 840698) because there was no English translation of the abstract and the document was in a foreign language.

Applicants respectfully request Examiner consider IDS document DE 840698 C. Document DE 840698 C was cited on the English language International Search Report (ISR) during the PCT phase of the instant application. A copy of the English language

ISR was filed as IDS document C8 on July 11, 2006, and was initialed as being considered by Examiner. The ISR indicated the degree of relevance found by the foreign office. Submission of an English language version of the search report that indicates the degree of relevance found by the foreign office satisfies the requirement for a concise explanation of relevance. 1138 OG 37, 38. Accordingly, it is proper that Examiner consider the document. The same is respectfully requested.

In addition, submitted herewith in a supplemental IDS is a translation of page 1, lines 1-24 of DE 840 698 as document NPL1. Consideration is respectfully requested.

The Drawings

Examiner requests new copies of at least Figures 1, 9 and 10. Applicants have provided replacement sheets for Figures 1, 9 and 10. Figure 1 is believed to be a better copy and no changes were made. For Figures 9 and 10, the black and shadowed interior of the bars in the bar charts of Figures 9 and 10 have been removed. Entry is respectfully requested.

The Abstract

Examiner objected to the abstract. A specific reason was not provided. Applicants note this is a PCT national stage entry and that WIPO publishes abstracts as page 1 of the published application. Accordingly, it is believed that perhaps an abstract page is missing in the Office's copy of the specification and that is the concern. Applicant attached herewith a separate abstract page for the instant specification. The text of this abstract is the same as that of the published PCT application.

The Specification

Examiner notes two typographical errors in the specification text and asks Applicants to review the same. Applicants have corrected the two errors noted by Examiner. Applicants have reviewed the specification and made additional corrections as indicated in the specification amendment section above.

The Objections to the Claims

Claims 57 and 77 are objected to as the drawing of the formula uses an identifier number 1 under the chemical structure that is in a different font style than that used in the text and in the dependent claims. Applicants have amended the recitation of the number next to the formula to be the same style as in the text and dependent claims. Only the font of the identification number is changed. The structure is not changed.

Also, Examiner asks Applicants to insert the term "a" in claim 77, line 2. Applicants have done so and thank the Examiner for noticing this.

The Rejections

The rejection under 35 U.S.C. § 112, first paragraph, for enablement

At Office action page 8, Examiner states that claims 57, 58, 63, 70-72, 74-80, 88 and 89 are rejected under 35 U.S.C. § 112, first paragraph, for enablement because the specification, while being enabling for a method for treatment of hypertriglyceridemia, does not reasonably provide enablement for the prevention of said disease. Applicants respectfully traverse this rejection. It is not required that the patient be maintained in a

hypertriglyceridemia state for the invention to work. A hypertriglyceridemia patient who begins treatment as claimed, and whose hypertriglyceridemia is treated by the claimed method, is also a patient the return of whose hypertriglyceridemia is being prevented by the claimed method. That is, the treatment for hypertriglyceridermia prevents, i.e., interferes with, the return of the hypertriglyceridemia.

However, in the interests of advancing prosecution, Applicants have amended the claims to refer to "treating" only. Accordingly, it is believed that this rejection can be withdrawn.

The rejection under 35 U.S.C. § 112, first paragraph, for written description

At Office action page 10, Examiner states that claim 77 is rejected under 35 U.S.C. § 112, first paragraph, for lack of written description. Examiner states the claim contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. Examiner states that the instant claim recites the limitation, "derivative," in reference to the instantly named compounds, and the exemplification in the specification is not a definition that allows the Examiner, or one of ordinary skill in the art, to ascertain that Applicants were in possession of the full scope of this genus. Applicants respectfully traverse this rejection.

Applicants have amended claim 77 to remove the word derivative and to refer to "said quaternary pyridinium salt." Accordingly, it is believed that this rejection can be withdrawn.

The rejection under 35 U.S.C. § 112, second paragraph

At Office action page 12, Examiner states that claim 77 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for recitation of "derivative." Applicants respectfully traverse this rejection.

Applicants have amended claim 77 to remove the word derivative and to refer to "said quaternary pyridinium salt." Accordingly, it is believed that this rejection can be withdrawn.

The rejections under 35 U.S.C. § 103

The first rejection under 35 U.S.C. § 103

At Office action page 13, claims 57, 58, 63, 74-76, 78 and 86-89 are rejected under 35 U.S.C. § 103 as being unpatentable over Carlson *et al., Atherosclerosis 16*:359-368 (1972), in view of Gębicki *et al., Polish J. Pharmacology 55*:109-112 (2003), as evidenced by Oettgen *et al., Cancer Res. 20*:1597-1601 (1960).

Carlson is relied on, *inter alia*, as disclosing a case of massive hypertriglyceridemia with fasting triglycerides, wherein nicotinic acid or nicotinamide was administered to reduce plasmic triglyceride levels to about 2-3 mmoles/L and raised the reduced levels of low-and high-density lipoproteins. Examiner states Carlson fails to disclose the specific formula I that comprises a methyl group at the 1-position, or where R is CH_3 or $N(H)CH_2OH$.

Gębicki is relied on, *inter alia*, as disclosing a homologue, or analog, 1-methylnicotinamide (MNA^+) as one of the two major primary metabolites of nicotinamide (NA).

Oettgen is relied on, *inter alia*, as disclosing charts wherein N-(hydroxymethyl)nicotinamide, instantly claims R is $N(H)CH_2CH_3$, and 3-acetylpyridine, wherien instantly claimed R is CH_3, were equally as potent as nicotinamide, wherein instantly claimed R is NH_2, and nicotinic acid.

Examiner states that a skilled artisan would have envisaged the instantly claimed formula I in the treatment of hypertriglyceridemia as disclosed by Carlson in view of Gębicki, as evidence by Oettgen, and that the artisan would have been motivated to combine the art when seeking a method for treating hypertriglyceridemia wherein a compound of formula I, with an increased efficacy at a specific dose and/or a reduction in undesirable side effects, is administered. Applicants respectfully traverse this rejection.

Respectfully, apparently, Examiner has made the assumption that from the mere fact that 1-methylnicotinamide is a metabolite of nicotinamide it follows that any known therapeutic action of nicotinamide should be exerted via its known metabolite, i.e. 1-methylnicotinamide. In other words, apparently the assumption has been made by Examiner that in the treatment of hypertriglyceridemia, nicotinamide (and nicotinic acid as well) is a "prodrug" of 1-methylnicotinamide.

Applicants respectfully disagree with the Examiner's findings. There is neither incentive nor motivation in the combined teachings of Gębicki and Carlsson for such assumption, for the following reasons.

Gębicki et al. disclose that 1-methylnicotinamide has use in the treatment of skin diseases by topical administration to the skin. Therefore, also any statements as to its safety, good tolerance, etc. would be viewed by a person skilled in the art in the context of such topical use. There is no motivation to extend this teachings to the use of MNA in lipids profile disorders. Such motivation cannot be found in Gębicki et al. – it could be found only in the present specification – such approach however, is only with having the benefit of Applicants' specification and therefore, is, however, an unallowable hindsight.

Indeed, it is stated in Gębicki et al. that in accordance with the then common general knowledge 1-methylnicotinamide is one of two major primary metabolites of nicotinamide. It is also stated that 1-methylnicotinamide is further metabolized to 2-PYR and 4-PYR. However, there is nothing in Gębicki to suggest that nicotinamide is inactive as such and would NOT exert its function disclosed in Carlsson et al. without earlier conversion to 1-methylnicotinamide. Such assumption, <u>if at all</u>, could only be made in contradiction with the then existing common general knowledge on the role and active forms of nicotinamide.

Any similarity of the structures between nicotinamide and MNA and other quaternary pyridinium salts of Formula I from the present application is only "superficial" and does not imply similarity of biological actions. The addition of a methyl group to the nitrogen atom of the pyridine ring of nicotinamide results in a

molecule that belongs to a different class of compounds, namely quaternary pyridinium salts, that, contrary to nicotinamide, have an ionic character and behave in a different manner in biological systems.

Having in mind the existing common general knowledge of the role of nicotinamide in living organisms and the mechanism of this role, the fact that MNA is the known metabolite of nicotinamide does not imply that nicotinamide exerts its function via MNA.

General knowledge is (and was at the date when the present invention was made) that nicotinamide (niacin, vitamin B3) is necessary for synthesis of NAD+ and NADP+ (nicotinamide adenine dinucleotide and nicotinamide adenine dinucleotide phosphate, respectively) which are active forms of nicotinamide (for the evidence see for example Harper's Biochemistry, Twenty-second edition., pages 549-551 (1990), copy provided on the accompanying IDS). This means that to exert its functions in a living body, nicotinamide must be first converted to NAD+ and NADP+. In order that such conversion could take place, nicotinamide must be first converted into nicotinate (nicotinic acid), as can be seen on the Scheme from Fig. 53-4, page 550 of Harper's Biochemistry. It can also be seen that 1-methylnicotinamide is shown on that Scheme as a metabolite not involved in any manner in transformations leading to biosynthesis of NAD and NADP. For these reasons this metabolite of nicotinamide for many years was considered inactive, as it was clearly stated in Gebicki et al., and the only known function thereof was as the marker of the level of nicotinamide in a body.

Furthermore, it should be noticed that also Carlson cited by the Examiner clearly mentioned in last two paragraphs on pages 366-367 that the effect of nicotinamide and nicotinic acid should be linked with NAD/NADH system (see the last sentence in the last paragraph:

> "further studies should be directed towards NAD(H) dependent esterifying processes in this and other cases of hypertriglyceridemia."

There is nothing in Carlson that could lead to any metabolite of nicotinamide other than nicotinic acid. On the contrary, because Carlson teaches that the same action is exerted by nicotinamide **AND** its metabolite nicotinic acid, one skilled in the art would link such action with the NAD system, as both these compounds are involved in this metabolic pathway. A person skilled in the art would not expect that 1-methylnicotinamide, which is <u>not</u> involved in the pathway leading to active forms of nicotinamide and which is considered to be *"a dead end"* of nicotinamide metabolism would have antihypertriglyceridemic action. On the contrary, the prior art teachings together with well established general knowledge concerning the role of nicotinamide in a living body, as discussed above and documented by Harper's Biochemistry, would lead him away from considering the use of 1-methylnicotinamide for such medical treatment. Antihypertriglyceridemic activity of 1-methylnicotinamide and its two analogues covered by Formula (I) could not be expected in view of Carlsson and Gębicki.

As it was stated in the specification of the present application, such an activity was found to be exerted through "vascular endothelium" and NOT by involvement in the metabolic pathway of niacinamide via nicotinate to NAD+/NADP+.

For the above reasons, the activity exerted by nicotinamide would not be linked by a person skilled in the art with its metabolite – 1-methylnicotinamide (MNA). In other words, the activity exerted by nicotinamide does not mean that 1-methylnicotinamide will have the same activity since this metabolite is not engaged in a chain of biochemical reactions leading to the nicotinamide active forms. All the more, it does not mean that it will have the same activity on its own, especially having regard the differences in the structure between this metabolite and its parent compound (the absence of nicotinate/carboxylate group and ionic character of MNA and its claimed analogues as salts).

Oetgen discloses that nicotinamide and nicotinic acid reversed the tumor inhibitory effect of 2-amino-13,4-thiadiazole and that the same effect was shared by 3-acetylpyridine and N-hydroxymethylnicotinamide. There is no mention of any activity of the the latter two compounds or their 1-methylated salts with respect to lipid profile, including antihypertriglyceridemic activity. In consequence, there is nothing in Oetgen that when added to the teachings of Carlson and/or Gebicki would lead the skilled person to the method of the present invention. Accordingly, *prima facie* nonobviousness is not established, or if it had been established, it has been overcome. Withdrawal of this rejection is believed proper, and is respectfully requested.

Therefore, claims 57, 58, 63, 74-76, and 86-89 are not obvious over Carlson, Gebicki and Oetgen, taken alone or in any combination.

The second rejection under 35 U.S.C. § 103

At Office action page 15, claims 70-72, 77, 79 and 80 are rejected under 35 U.S.C. § 103 as being unpatentable over Carlson *et al., Atherosclerosis 16*:359-368 (1972), in view of Gębicki *et al., Polish J. Pharmacology 55*:109-112 (2003), as evidenced by Oettgen *et al., Cancer Res. 20*:1597-1601 (1960), as applied above, and further in view of Bova *et al.,* WO 99/06046, and Mathias, U.S. Patent No. 7,153,870 B2.

Carlson, Gębicki and Oettgen are relied on as above. In addition, Bova is relied on as disclosing a method for altering lipids in an individual without causing drug-induced hepatotoxicity, myopathy or rhabdomyolysis, wherein the method comprises administering to the individual once per day a single dose of a pharmaceutical combination comprising an effective lipid-altering amount of an HMG-CoA reductase inhibitor, a cardiovascular agent.

Examiner states that a skilled artisan would have envisaged the instantly claimed method of treating hypertriglyceridemia, administering a quaternary pyridinium salt of formula I in combination with a cardiovascular agent as disclosed by Boa, through customary routes, i.e., oral, parenteral and inhalation, known to one of ordinary skill, as disclosed by Mathias. Examiner states that one of ordinary skill would have been motivated to combine the teachings of the aforementioned references when seeing a combination therapy for the treatment of hypertriglyceridemia and that it would have been obvious to one of ordinary skill in the art, at the time of the invention, because the combined teachings of the prior art are fairly suggestive of the claimed invention. Applicants respectfully traverse this rejection.

Bova et al., while teaching combinations of nicotinamide with other cardiovascular agents, does not detract from the nonobviousness of claims 70-72, 77, 79 and 80, even when considered in combination, since all these claims are dependent on claim 57 and require the use of 1-methylated pyridinium salt of Formula I, the non-obviousness of which was discussed above.

Mathias et al. disclose different modes of administration of nicotinamide derivatives that are not related in any manner with quaternary salts of the present Formula I. Mathias et al. do not detract from the nonobviousness of claims 70-72, 77, 79 and 80, even when considered in combination, since all these claims are dependent on claim 57 and require the use of 1-methylated pyridinium salt of Formula I, the non-obviousness of which was discussed above.

Accordingly, *prima facie* nonobviousness is not established, or if it had been established, it has been overcome. Withdrawal of this rejection is believed proper, and is respectfully requested.

The provisional rejections for obviousness type double patenting

The first provisional rejection for obviousness type double patenting: 11/484,892

At Office action page 18, claims 57, 58, 63, 75-79 and 86-89 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 13-15, 19, 22-25, 37, 53 and 54 of copending application no. 11/484,892. Examiner states that the claims are not patentably distinct because the '892

claims a method of treating, orally, a lipoprotein abnormality, i.e., hyperlipidemias, which includes hypertriglyceridemia, in a subject in need thereof by administering to the subject a food extract containing N-methylnicotinamide, and the instant application claims 1-methylnicotinamide. Examiner states that to those skilled in the chemical art, one homologue is not an advance over an adjacent member of a homologous series. Applicants respectfully traverse this rejection.

Applicants respectfully draw Examiner's attention to the fact that these two applications are not commonly assigned. Also, the filing date of 11/484,892 (July 11, 2006) is after Applicants' PCT filing date of January 7, 2005. Applicants respectfully request that the rejection be held in abeyance until the claims are otherwise allowable and then that this, the first filed application be allowed to proceed to issuance. As noted at MPEP 804(I)(B)(1):

> If a "provisional" nonstatutory obviousness-type double patenting (ODP) rejection is the only rejection remaining in the earlier filed of the two pending applications, while the later-filed application is rejectable on other grounds, the examiner should withdraw that rejection and permit the earlier-filed application to issue as a patent without a terminal disclaimer.

The second provisional rejection for obviousness type double patenting: 11/874,627

At Office action page 19, claims 57, 58, 63, 70, 75, 78, 80 and 86-89 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 5, 6 and 8 of copending application no. 11/874,627. Examiner states that the claims are not patentably distinct because the '627 claims a

method of treating a lipoprotein abnormality, i.e., hyperlipidemias, which includes hypertriglyceridemia, in a subject in need thereof by administering to the subject a pharmaceutical composition comprising a statin, which is a cardiovascular agent (see claim 77) and a compound of Formula I, wherein R may be NR_2R_3, wherein R_2 is hydrogen and R_3 is either hydrogen or CH_2OH. R_1 is methyl and X- is a physiologically suitable counter-anion. Examiner states that in the instant excerpt, the '892 application further claims a method of raising HDL-cholesterol levels in a subject in need thereof by administering to the subject a pharmaceutical composition comprising a statin and a compound of Formula I. Applicants respectfully traverse this rejection.

Applicants respectfully draw Examiner's attention to the fact that these two applications are not commonly assigned. Also, the filing date of 11/874,627 (October 18, 2007) is after Applicants' PCT filing date of January 7, 2005. Applicants respectfully request that the rejection be held in abeyance until the claims are otherwise allowable and then that this, the first filed application be allowed to proceed to issuance. As noted at MPEP 804(I)(B)(1):

> If a "provisional" nonstatutory obviousness-type double patenting (ODP) rejection is the only rejection remaining in the earlier filed of the two pending applications, while the later-filed application is rejectable on other grounds, the examiner should withdraw that rejection and permit the earlier-filed application to issue as a patent without a terminal disclaimer.

Conclusion

It is respectfully believed that a full and complete reply to the Office action has been made and that this application is now in condition for examination. Early notice to this effect is respectfully requested.

Respectfully submitted,

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